

INTRODUCTION & OBJECTIVES

- GAD is defined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), as a condition characterized by excessive anxiety and worry occurring for at least six months, causing significant distress or impairment¹
- Despite the extensive literature published on GAD, there exists an unmet need to address the burden of illness with the current disease management practices; patients with GAD often report diminished quality of life characterized by persistent anxiety, difficulty in daily functioning, increased healthcare utilization and cost of care, including more frequent visits to healthcare providers and therapy sessions^{2,3}
- Data presented reflects an interim analysis (literature published between 2019-2024) of a comprehensive literature review, which captures 20 years of literature (2004-2024) in GAD to assess and characterize GAD symptoms, clinical manifestations, comorbidities, and evaluate the impact of GAD on the activities of daily living (ADLs) and quality of life (QoL)

METHODS

- The SLR was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist
- Systematic searches in PubMed and Embase were performed using predefined search terminologies focusing on epidemiology, clinical outcomes, economic outcomes, or humanistic outcomes in GAD (**Table 1**)
- Manuscripts and conference abstracts, published from November 1st, 2019, to November 11th, 2024, meeting the eligibility criteria were included
- Identified articles were uploaded to an artificial intelligence (AI)-enhanced platform used to facilitate the SLR process; duplicates across the databases were removed in the platform (**Figure 1**)
- Title/abstract screening was conducted per the defined population, intervention, comparator, outcomes, and study design (PICOS) criteria by one human researcher in parallel with one AI screener providing reviewer-level decisions; adjudication was performed by an independent human researcher
- In line with the ISPOR guidelines on the AI use for SLRs, the validated AI screening platform was initially trained using 50 adjudicated screening decisions and 10 inclusions before activation, and continued to improve its performance through subsequent screening
- After screening, full texts were retrieved and screened by two independent human reviewers, facilitated via the AI platform; data from included studies were extracted in a Microsoft Excel™ grid

Table 1 | Overview of Key Search Terms

CATEGORY	OVERVIEW OF KEY SEARCH TERMS
Epidemiology	Prevalence OR Incidence OR Guideline OR Diagnosis OR Disease management OR Treatment pattern
Clinical Outcome	Symptom OR Severity OR Prognosis OR Generalized anxiety disorder scale OR Treatment preference OR Safety OR Dose-response
Economic Outcome	Cost of illness OR Health expenditure OR Cost effectiveness OR Healthcare resource OR Productivity OR Indirect cost OR Caregiver cost
Humanistic Outcome	Patient reported outcome OR Quality of life OR Patient satisfaction OR QALY OR DALY OR Activities of Daily living OR Patient assessment

RESULTS

Figure 1 | PRISMA Flow Diagram of Study Selection

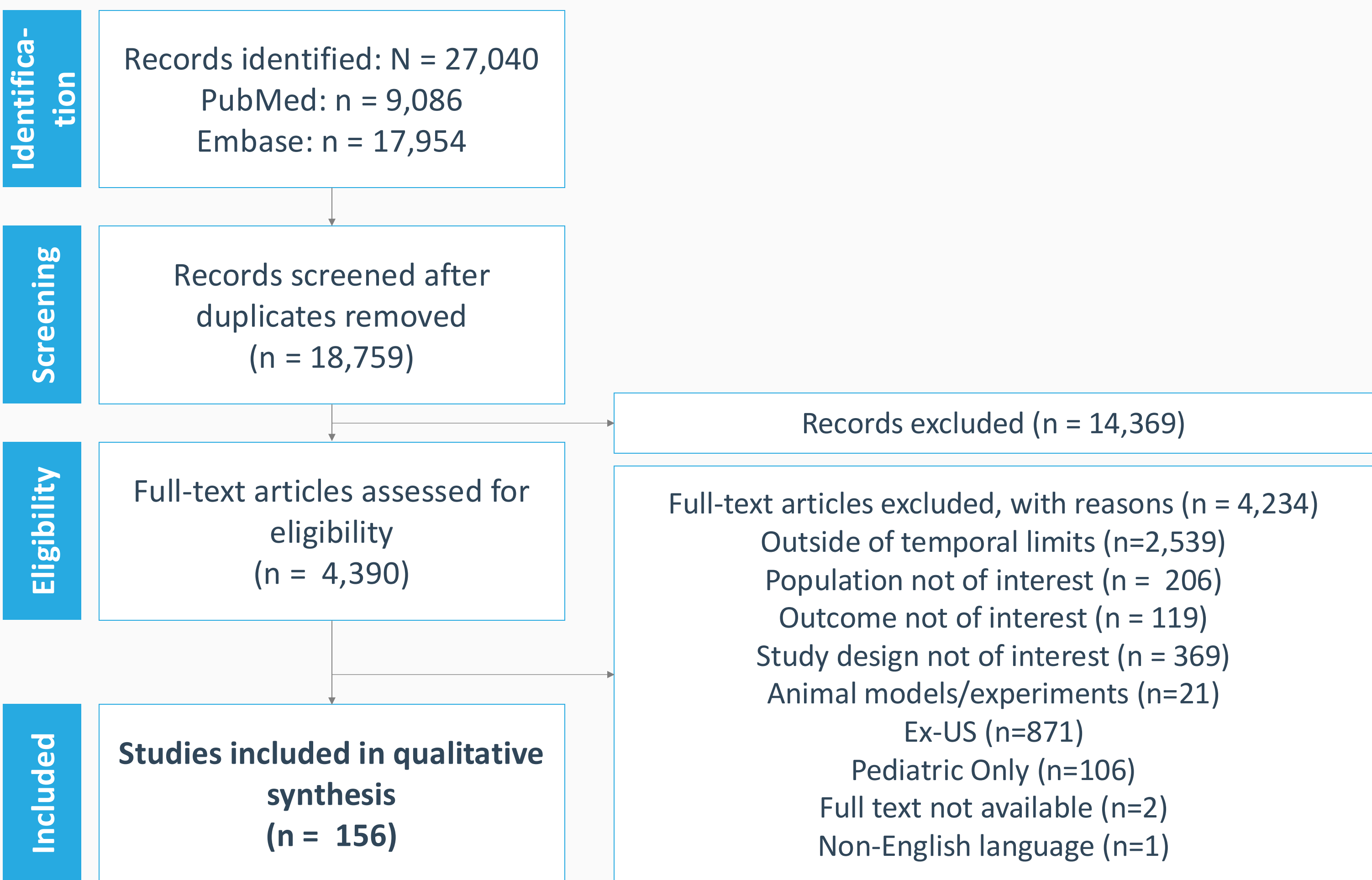
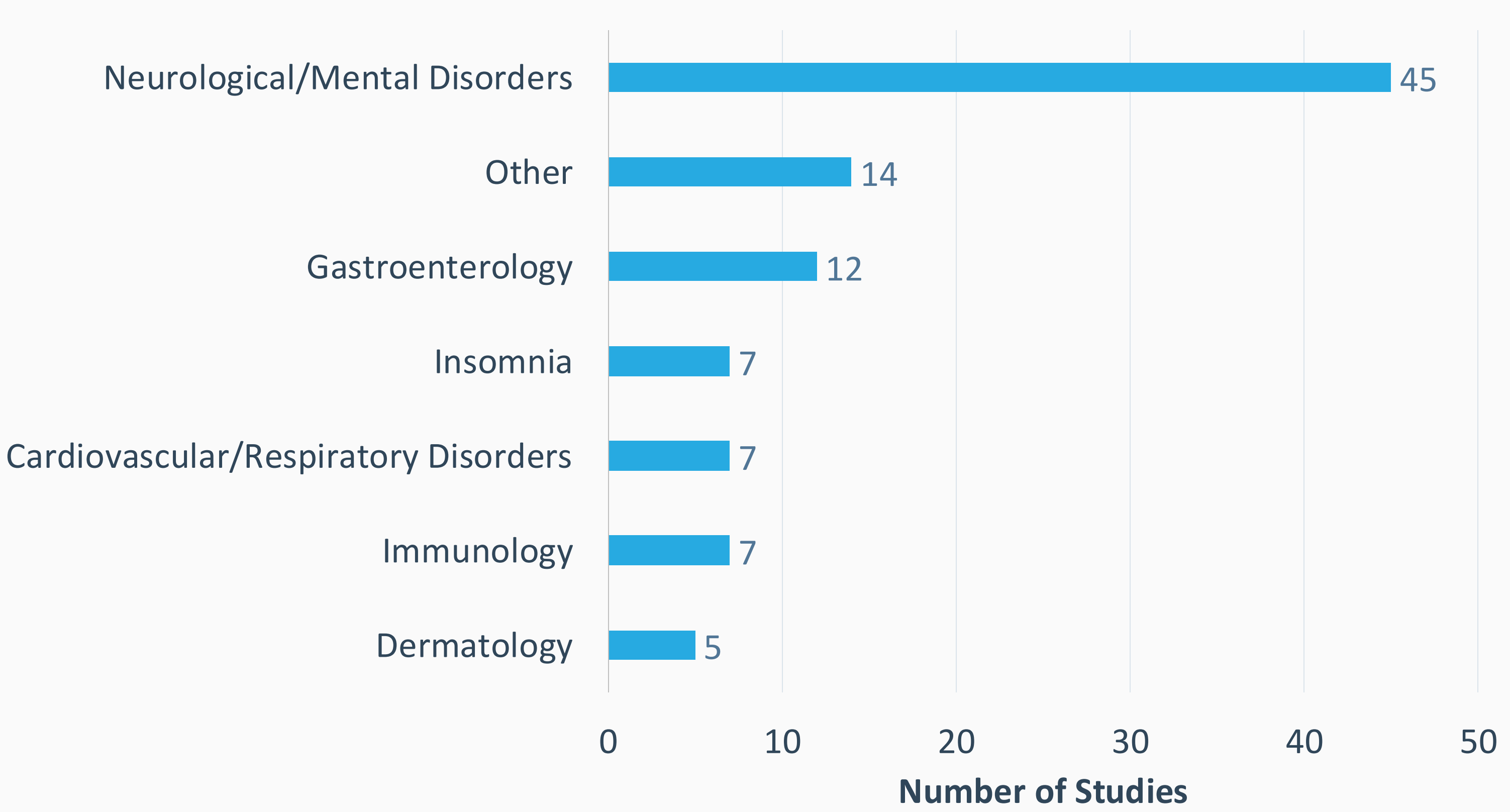


Figure 2 | Study Topics

Topic Name	Frequency of Studies
GAD Primary/Secondary Epidemiology	123
GAD Comorbidities	105
Humanistic Burden of GAD	62
GAD Clinical manifestations	52
GAD DSM V Symptoms	43

*The sum of the studies is higher than 156, as one study may provide data on more than one topic

Figure 3 | Frequency of Conditions Co-occurring with GAD



- Comorbid GAD in patients with pancreatitis, morbid obesity, and those with OCD are associated with worsened outcomes, including increased risk of mortality, increased risk of treatment failure, increased suicide risk, and higher admission rates⁴⁻⁷
- In patients with respiratory disease, bacterial infections, and HIV, GAD was associated with increased likelihood of experiencing delirium in ICU patients, alters gut microbiota, lowers the remission rate, and increases risk of new-onset cardiovascular disease⁸⁻¹⁰

Table 2. List of Conditions Captured as GAD Comorbidities

Mental Disorders	Gastroenterology ^{49,50}	Other	Immunology
Bipolar Disorder ¹¹ BPD ¹² Depression ¹³⁻¹⁵ Eating Disorder ¹⁶⁻¹⁸ Hoarding Disorder ^{19,20} MDD ²¹⁻³⁷ OCD ^{5,38,39} PTSD ⁴⁰ SAD ⁴¹ Substance use ^{42-46,74} Suicidal ideation ⁴⁷ Trichotillomania ⁴⁸	Chronic pancreatitis ⁴ C. Difficile Infection ⁹ Diverticulosis ⁵¹ Gastrointestinal bleed ⁵² Mallory Weiss Syndrome ⁵³ Gastroparesis ⁵⁴ GERD ⁵⁵ IBD ^{*56,57} IBS ⁵⁸	Cancer ⁵⁹⁻⁶¹ Pregnancy ⁶²⁻⁶⁵ Trauma ⁶⁶ Surgery ^{6,67,68} Chronic Diseases ^{37,69,70}	Allergy ⁷¹ Dermatomyositis ⁷² HIV ⁷³⁻⁷⁶ Celiac Disease ⁺⁷⁷
		Cardiovascular ⁸⁹	Neurology
		Coronary Artery Disease ⁸ Peripartum Cardiomyopathy ⁹⁰ Aneurysm ⁹¹	Alzheimer’s Disease ⁸³ Mal de Debarquement Syndrome ⁸⁴ Migraine ⁸⁵
	Dermatology		Respiratory
	Alopecia ⁷⁸ Skin-picking disorder ⁷⁹⁻⁸¹ Vitiligo ⁸²		Asthma ⁸⁶ Acute Respiratory Distress Syndrome ^{87,88}

*IBD is an autoimmune disease and can be grouped with immunology disorders; +Celiac disease can have dermatological and gastrointestinal manifestations
Note: The most common GAD comorbidities are **bolded** in Table 2

- Numerous conditions occur as GAD comorbidities and vice versa, highlighting the complexity of diagnosing and treating GAD in these patients (**Figure 3 and Table 2**)
- GAD and major depressive disorder (MDD) are highly comorbid, with an estimated 62% of GAD patients reporting a MDD episode in their lifetime⁶⁹; this relationship is mediated by factors including poor sleep quality, poor quality of life, additional psychiatric disorders, social adjustment problems, etc.^{25,27}
 - Current literature often reports outcomes for a heterogeneous population of patients with GAD or MDD, though it is unclear which outcomes are a direct result of either indication

GAD Symptoms

- Elevated Anxiety and Depression:** Patients with GAD show significantly higher levels of anxiety, stress, and depression^{14,38,92,105}
- Neuroticism:** Young adults with high neuroticism have a 33.93% incidence of GAD, compared to 17% for MDD⁹³
- Self-injury:** GAD is associated with the subsequent onset and higher severity of non-suicidal self-injury⁹⁴
- Sleep Disturbances:** Patients with GAD often report insomnia symptoms and poor sleep quality⁹⁵⁻¹⁰¹

GAD Clinical Manifestation

- Cognitive and Motor Deficits:** GAD patients underperform in information processing, motor skills, verbal, and visuospatial functions⁹²
- Psychophysiological Parameters:** Upon stress removal, patients with GAD had reduced heart rate recovery compared to healthy patients¹⁰²

Impact on Quality of Life (QoL) and Activities of Daily Living (ADLs)

- Health-Related Quality of Life:** When compared to healthy controls, GAD patients reported significantly reduced QoL; greater impairment in patients with more severe anxiety symptoms or additional comorbidities^{69,103}

Healthcare Resource Utilization (HCRU)

- Increased and Inconsistent Resource Use:** The co-occurrence of GAD with other disease conditions significantly increases the likelihood of missed routine appointments, higher number of emergency or urgent care visits, prolonged hospital stays, greater incidence of complications, and reduced adherence to medications^{44,51-54,56,104}

DISCUSSION AND CONCLUSIONS

- This SLR serves as an interim of a comprehensive analysis of GAD literature published over the past 20 years; results presented herein specifically capture data from observational studies/non-RCT/clinical trial reports published in the US within the last 5 years (2019-2024)
- The high degree of comorbidity among patients with GAD complicates the diagnosis and treatment of GAD
- Literature in GAD is extensive, but little progress has been made to translate this knowledge base into increased disease-state awareness or improved patient outcomes
- A comprehensive review of articles published over the past 20 years will generate a foundational resource to inform key gaps in our understanding and perception of GAD (e.g., patient journey, impact on QOL, current treatment paradigms, existing burden despite treatments, etc.)

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ABBREVIATIONS

- ADL: Activities of Daily Living
- AI: Artificial Intelligence
- BPD: Borderline Personality Disorder
- C. Difficile: Clostridium Difficile
- DALY: Disability-Adjusted Life Year
- DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
- GAD: Generalized Anxiety Disorder
- GERD: Gastroesophageal Reflux Disease
- HCRU: Healthcare Resource Utilization
- HIV: Human Immunodeficiency Virus
- HRQoL: Health-related Quality of Life
- IBD: Inflammatory Bowel Disease
- IBS: Irritable Bowel Syndrome
- ICU: Intensive Care Unit
- MDD: Major Depressive Disorder
- OCD: Obsessive Compulsive Disorder
- PICOS: Population, Intervention, Comparator, Outcomes, and Study Design
- PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
- PTSD: Post-Traumatic Stress Disorder
- QALY: Quality-Adjusted Life Year
- QoL: Quality of Life
- RCT: Randomized Controlled Trial
- SAD: Social Anxiety Disorder
- SLR: Systematic Literature Review
- US: United States